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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,366	12/13/2001	Richard John Bazin	PC10934AGPR	3340

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 01/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/022,366	BAZIN ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2005 and 17 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Appendix A*.

DETAILED ACTION

Application Status

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656. Claims 1 and 3-20 are pending in the application. Applicant's amendment to the claims, filed on 6/27/2005, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims. Applicant's amendment to the specification, filed on 10/17/2005, is acknowledged. Receipt of an information disclosure statement (IDS), filed on 6/27/2005, is acknowledged. Receipt of a statement that the sequence listing filed on 6/6/2002 contains no new matter is acknowledged. Applicant's arguments filed on 6/27/2005 in response to the non-final Office action mailed on 2/24/2005 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Information Disclosure Statement

All references cited in the IDS filed on 6/27/2005 have been considered by the examiner. A copy of Form PTO-1449 is attached to the instant Office action.

Objections to the Specification

The specification is objected to because the instant specification amendment does not correspond to the page and line numbers of the specification filed on 12/13/2001. Appropriate correction is required.

Claim Objections

Claim 4 is objected to in the recitation of "P4.sub.22.sub12." It is suggested that applicant replace "P4.sub.22.sub12" with the notation that is used throughout the specification (see, *e.g.,* specification at p. 5, l. 13), *i.e.,* $P4_22_12$.

Claims 10 and 14 are objected to in the recitation of ".ANG." It is suggested that applicant replace ".ANG." with the notation that is used throughout the specification (see, *e.g.,* specification at p. 5, l. 14), *i.e.,* Å.

Claim 11 is objected to in the recitation of "(.beta..alpha.)sub.8." It is suggested that applicant replace "(.beta..alpha.)sub.8." with the notation that is used throughout the specification (see, *e.g.,* specification at p. 5, l.), *i.e.,* $(\beta\alpha)_8$.

Claims 12-13 are objected to as reciting an improper sequence identifier, which should be replaced with "SEQ ID NO:2." See 37 CFR 1.821(d).

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claims 1 and 3-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 (claim(s) 3-20 dependent therefrom) recites the limitation "the AMPDA catalytic domain." There is insufficient antecedent basis for this limitation in the claim.

Furthermore, it is unclear as to the sequence or sequences that are intended as being encompassed by the term "the AMPDA catalytic domain." It is suggested that applicant clarify the meaning of the term.

b. Claim 14 is indefinite in the recitation of "diffracts X-rays to 3.5 Å or higher resolution" as it is unclear as to whether the term is meant to be interpreted as meaning the crystal diffracts X-rays to (3.5 Å or higher) resolution, *i.e.,* a resolution of a number greater than 3.5 Å, or the crystal diffracts X-rays to 3.5 Å or (higher resolution), *i.e.,* a resolution of a number less than 3.5 Å. It is suggested that applicant clarify the meaning of the claim.

c. The meaning of the term "the primary sequence" in claim 20 is unclear. For example, is the term meant to refer to the amino acid sequence of the AMPDA or some subsequence of the AMPDA? It is suggested that applicant clarify the meaning of the term.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

The written description rejection of claims 1 and 3-20 under 35 U.S.C. § 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the genus of AMPDA crystals is sufficiently described because all members of the genus of crystals has the common structural characteristics of an isolated AMP protein crystal and a tetragonal shape.

According to applicant, that the genus of crystals has a tetragonal shape is sufficient to distinguish the genus from other AMPDA crystals.

Applicant's argument is not found persuasive. While it is acknowledged that all members of the genus of crystals has an AMPDA polypeptide and has a tetragonal shape, these characteristics are insufficient to describe all members of the claimed genus. First, it is noted that the recitation of "[a]n isolated AMP deaminase...crystal consisting essentially of the AMPDA catalytic domain" fails to provide a sufficient description of the recited genus of AMPDA proteins as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." Similarly with the recited genus of proteins the functional definition of the genus does not provide any structural information commonly possessed by members of the genus that distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus.

Regarding the structure of the crystal itself, the Court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." UC California v. Eli Lilly, (43 USPQ2d 1398). For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.,* structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. At the time of the invention, it was well-known in the art that the structure of a protein crystal was defined by three repeating vectors a, b, and c, with angles α, β, and γ, between them. See pp. 586 and 2725 of the "Encyclopedia of Molecular Biology" (Creighton, T., John Wiley and Sons, Inc. New York, 1999).

The specification discloses only three representative species of the genus of claimed crystals (specification Examples 3 and 5 at pp. 12-14 and 18-20). Other than

these three species, the specification fails to disclose any other representative species of the claimed genus of crystals, which encompasses widely variant crystals having any space group, unit cell dimensions, and/or any sequence of an AMPDA, optionally wherein the sequence is SEQ ID NO:2. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus," it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." The structures of the crystals (unit cell dimensions and space group), with the exception of being tetragonal, and/or the polypeptides of the crystals are essentially undefined and thus, encompass widely variant species. Even though applicant may argue that all members of the claimed genus of crystals has a tetragonal shape, it should be noted that numerous space groups are included within the "tetragonal" crystal system as evidenced by Appendix A, further supporting the examiner's position that the genus encompasses widely variant species.

Given the lack of description of a representative number of protein crystals, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

The scope of enablement rejection of claims 1 and 3-20 under 35 U.S.C. § 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the claims are limited to crystals of the AMPDA catalytic domain, which, according to applicant, is highly conserved, thus enabling a skilled artisan to use the specification's guidance to crystallize all AMPDA catalytic domains without undue experimentation.

Applicant's argument is not found persuasive. The claims broadly encompass a crystal of any AMPDA catalytic domain, having any sequence of amino acids (optionally complexed with any ligand), any space group, and/or any unit cell dimensions. While applicant asserts the AMPDA catalytic domain is highly conserved, there is no evidence in the application file of such conversation among the members of the AMPDA family. Even assuming *arguendo* the "catalytic domain" of AMPDA is highly conserved, it is noted that the claims are not limited to those AMPDA catalytic domains that *are* highly conserved, but additionally encompass mutants and variants of known AMPDA catalytic domains. Also, that the domain is highly conserved and not identical indicates that the sequences of the catalytic domains are variable. As recognized by Kierzek et al. (*Biophys Chem* 91:1-20), "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). Thus, in view of the teachings of Kierzek et al., a skilled artisan would recognize the high level of unpredictability associated with using the disclosed crystallization conditions (Examples 3 and 5) for crystallizing other AMPDA catalytic domains. Applicant may argue that, if the disclosed crystallization conditions do not suffice for a diffraction quality crystal,

other crystallization conditions can be routinely determined. However, this is not the case. For example, Branden et al. ("Introduction to Protein Structure," Branden and Tooze, Garland Publishing Inc., New York, 1999) teaches that even minor alterations in the crystallization parameters can affect crystallization because the formation of protein crystals is critically dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions and ligands to the protein (page 375, middle). Branden et al. further teaches that altering crystallization parameters can cause the molecules to pack in different ways to produce different crystal forms (page 375, bottom). Further, it is noted that one cannot predict *a priori* those crystallization conditions that will achieve a particular shape, namely a tetragonal shape in this case. For example, the specification discloses that other crystals of AMPDA from rabbit skeletal muscle are hexagonal bipyramidal (p. 3, ll. 15-16). Even if the disclosed crystallization conditions were sufficient to achieve AMPDA catalytic domain crystallization, as evidenced by the specification, not all crystals of AMPDA are of diffraction quality (specification at p. 3, ll. 15-16) and it is highly unpredictable as to whether crystals of other AMPDA catalytic domains generated using the disclosed crystallization conditions would be of such quality. The state of the art at the time of the invention acknowledges the high level of unpredictability for making diffraction quality crystals, particularly those that diffract to a resolution greater than the disclosed 2.2 Å or 2.5 Å resolution. For example, Branden et al. (*supara*) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "[w]ell-ordered crystals...are difficult to grow.." (p. 374) and further teaches that

while there are instances where the structure of a protein has been resolved to a resolution of 1 Å, "only a few small proteins have been determined to such high resolution" (p. 382, first full paragraph). While the specification discloses three working examples of crystallization of the same polypeptide with or without ligand (specification Examples 3 and 5 at pp. 12-14 and 18-20), the specification fails to provide the necessary guidance for crystallizing other AMPDA catalytic domain polypeptides with or without ligand with an expectation that these crystals will be of diffraction quality. In this case, one is left to trial-and-error experimentation to attempt to make all crystals as broadly encompassed by the claims without the necessary guidance. Such experimentation was not routine at the time of the invention. In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make all methods and crystals as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Conclusion

Status of the claims:

- Claims 1 and 3-20 are pending.
- Claims 1 and 3-20 are rejected.
- No claim is in condition for allowance.

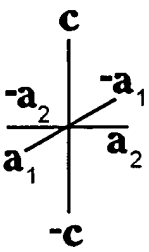
Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-

272-0942. The examiner can normally be reached on Mon to Thurs, 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656

Tetragonal 	Tetragonal - Disphenoidal	($\bar{4}$)	$I\bar{4}$ and $P\bar{4}$	P = Primitive Lattice. I = Body Centered Lattice. $\bar{4}$ = Rotoinversion Axis. 4,2 = Symmetry Axis (360/n). $4_{1,2,3}$ = Screw Axis. a,b,c = Perpendicular Glide Planes. m,n = Oblique Glide Planes.
	Tetragonal - Pyramidal	(4)	I4, $I4_1$, P4, $P4_1$, $P4_2$, and $P4_3$	
	Tetragonal - Dipyramidal	(4/m)	I4/m, $I4_1/a$, P4/m, P4/n, $P4_2/m$, and $P4_2/n$	
	Tetragonal - Scalenohedral	($\bar{4}$ 2m)	$I\bar{4}2d$, $I\bar{4}2m$, $I\bar{4}c2$, $I\bar{4}m2$, $P\bar{4}21c$, $P\bar{4}2_1m$, $P\bar{4}2c$, $P\bar{4}2m$, $P\bar{4}b2$, $P\bar{4}c2$, $P\bar{4}m2$, and $P\bar{4}n2$	
	Tetragonal - Ditetragonal Pyramidal	(4mm)	I4/mcm, I4/mmm, $I4_1/acd$, $I4_1/amd$, P4/mbm, P4/mcc, P4/mmm, P4/mnc, P4/nbm, P4/ncc, P4/nmm, P4/nnc, $P4_2/mbc$, $P4_2/mcm$, $P4_2/mmc$, $P4_2/mnm$, $P4_2/nbc$, $P4_2/ncm$, $P4_2/nmc$, and $P4_2/nnm$	
	Tetragonal - Trapezohedral	(4 2 2)	$I4_122$, I422, $P4_12_12$, $P4_122$, $P42_12$, P422, $P4_22_12$, $P4_222$, $P4_32_12$, and $P4_322$	
	Tetragonal - Ditetragonal Dipyramidal	(4/m 2/m 2/m)	$I4_1cd$, $I4_1md$, I4cm, I4mm, $P4_2bc$, $P4_2cm$, $P4_2mc$, $P4_2nm$, P4bm, P4cc, P4mm, and P4nc	